REMARKS/ ARGUMENTS

Applicant has carefully studied the non-final Examiner's Action mailed December 8, 2011, having a shortened statutory period for response set to expire March 8, 2012. The amendment appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Claim Rejections - 35 U.S.C. § 112

Paragraph 1

Office has rejected claims 1-5, 17, and 20 under 35 U.S.C § 112, first paragraph, for failing to satisfy the written description requirement. The Office found the Application provides adequate description for reducing aspirin-induced gastric lesions through administration of L-deprenyl, a combination of aspirin and L-deprenyl, and a combination of aspirin and propargyline.[1] The Office went on to state that there is not adequate description of preventing, reducing or reversing aspirin-induced lesions through administration of a MAO inhibitor.[2] Applicant notes that the Application provides that MAO-B inhibitors provide free radical scavenging, upregulation of growth factors like NGF, vasodilation and increased blood flow, and stimulation of constitutive nitric oxide.[3] The prevention of GI damage is seen to stem from these properties, along with inhibition of platelet activation. [4]

Aspirin and non-aspirin NSAIDS inhibit COX, which is involved in prostaglandin generation, and is produced by the gastric mucosa.[5] Prostaglandins provide cytoprotective function, and form a gastric mucosal barrier, which includes the maintenance of gastric blood flow during exposure to a noxious substance, secretion of bicarbonate and mucus by the surface epithelial cells, and the rapid repair of superficial injury through the process of epithelial restitution.[6] Further,

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[1] Page 6 of the non-final Office Action, dated December 8, 2011.
[2] Page 6 of the non-final Office Action, dated December 8, 2011.
[3] Page 9, lines 1-11 of the Application.
[4] Page 17, lines 17-25 of the Application.
[5] Fiorucci. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. Gastroenterol Clin North Am. 2009 Jun;38(2):315-32; page 315.
[6] Fiorucci. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. Gastroenterol Clin North Am. 2009 Jun;38(2):315-32; page 315.

> NO is now recognized as one of the most important of such mediators in the human body, mediating blood flow, neurotransmission, immune reactions, and muscle contraction[.] … Since the early 1990s, a body of evidence supports the notion that acute gastric injury in animal models of NSAID gastropathy is a neutrophil-dependent process. Rats that had been immunodepleted of their circulating neutrophils develop very little gastric damage when given NSAIDs at doses that, in normal rats, caused widespread hemorrhagic lesions. Moreover, interfering with the adherence of neutrophils to the vascular endothelium, through the administration of monoclonal antibodies directed against leukocyte or endothelial adhesion molecules, also greatly reduced the severity of NSAID-induced gastric damage. We were the first in the middle of the 1990s to demonstrate that NSAIDs trigger leukocyte adherence to the vascular endothelium though a mechanism that requires the release of tumor necrosis factor alpha (TNF-a), and administration of TNF-a antagonists or inhibitors protects against the gastric toxicity induced by ns-NSAIDs. In the same period of time, NO was demonstrated to be an important modulator of adhesive interactions between leukocytes and the vascular endothelium. This raised the possibility that the protective effects of NO that had been observed in experimental models of gastric damage might be in part due to its ability to inhibit leukocyte-endothelial adhesion.[7]

As such, nitric oxide releasing NSAIDS were developed to provide gastroprotection, but have limited use as the NO released from such drugs is quickly degraded, with a half-life of less than 30 seconds.[8]

However, the present invention stimulates NO production using MAO inhibitors. MAO inhibitor pretreatment was also found to inhibit activation of leukocytes and platelets.[9] Moreover, Applicant notes that the Application provides

> [t]he rat gastric lesion test as described previously (Kiragawa et al; 1990 and Alghamdi et al; 1991) was used to examine the ability of test compounds to produce gastric lesion. Male Sprague-Dawley rats weighing 250-300 g were deprived of food for 24 hours, with free access to water and then dosed by oral gavage with solvent or drugs given at a volume of 0.5 ml / 100 g body weight. For the unmodified NSAIDS being given in combination with a MAO inhibitor, the MAO inhibitor was administered by oral gavage immediately prior to the administration of NSAID by oral gavage. … For investigating the reversal of NSAID induced gastric lesion, following 8 hours after NSAID dosing the animals were provided food and water ad libitum. They were treated daily with oral gavage of MAO inhibitor for 7 days. These animals were then euthanized and the

[7] Fiorucci. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. Gastroenterol Clin North Am. 2009 Jun;38(2):315-32; page 319-320 (citations deleted).
[8] Page 5, lines 1-14 of the Application; Fiorucci. Prevention of nonsteroidal anti-inflammatory drug-induced ulcer: looking to the future. Gastroenterol Clin North Am. 2009 Jun;38(2):315-32; page 316.
[9] Page 21, lines 16-21 of the Application.

> stomachs examined for the presence of lesions. After euthanizing, the stomachs were dissected along the greater curvature, rinsed with saline to remove the debris, the cleaned tissue was pinned open in a dish, covered with saline and examined for hemorrhagic lesions. Gastric lesions per mm were calculated by adding the lesions in the observed area. … The NSAIDS produced significant gastrointestinal lesion (table 3). **Pretreatment with l-deprenyl provided protection against NSAID induced gastric lesion.** The NSAID attached to the MAO inhibitor also attenuated the gastric toxicity of NSAIDS. The **gastric lesions were also reversed by daily administration of l-deprenyl for 7 days**. The ability of MAO inhibitors to protect the gastrointestinal tissue form cytotoxic damage is clearly demonstrated.[10]

As seen from the emphasized sections, the Applicant specifically discusses use of the MAO inhibitors to prevent gastric lesion, through pretreatment of MAO inhibitor prior to administration of NSAIDS, and the reversal of damage by administering MAO inhibitor for 7 days after the administration of NSAIDS.

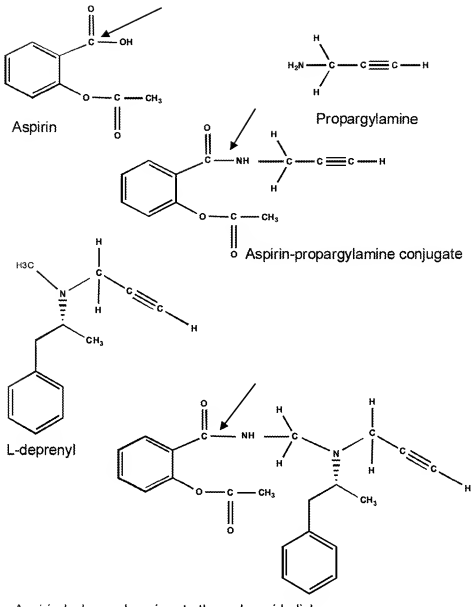
Applicant therefore submits that the Application provides dosing for the prevention and reversal of NSAID damage. Further, amounts of MAO inhibitor to NSAID are also provided in the Application, as evidenced on page 19, lines 3-10.

Accordingly, Applicant respectfully requests the Office withdraw the 35 U.S.C § 112, first paragraph written description rejection of claims 1-5, 17, and 20.

Paragraph 2

Claims 17 and 20 stand rejected under 35 U.S.C § 112, second paragraph as indefinite. The Office noted that claim 20 includes the term "general", which the Office found lacks probative value.[11] Additionally, the claim provides for an amide, which the Office found consists of a carbonyl linked to nitrogen.[12] Applicant points out that aspirin, propargylamine, and deprenyl have the following structures, along with their conjugates;[13]

[10] Page 22, lines 15 to page 23, line 13 of the Application (emphasis added).
[11] Page 5 of the non-final Office Action, dated December 8, 2011.
[12] Page 5 of the non-final Office Action, dated December 8, 2011.
[13] http://en.wikipedia.org/wiki/Aspirin (last accessed March 6, 2012); http://www.sigmaaldrich.com/catalog/ProductDetail.do?D7=0&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&N4=P50900%7CALDRICH&N25=0&QS=ON&F=SPEC (last accessed March 6, 2012); http://en.wikipedia.org/wiki/Selegiline (last accessed March 6, 2012).



As seen from the arrow, aspirin has a carbonyl group attached to the benzene ring. Further, the conjugation of aspirin and progargyline have an amide bond, which the Office found comprises R-(C=O)-N.[14] Likewise, aspirin and deprenyl also show an amide bond, highlighted by the arrow. It is therefore submitted that the claims are clear to one of skill in the art.

[14] Page 5 of the non-final Office Action, dated December 8, 2011.

The Office found claim 17 lacks antecendent basis from claim 1, which recites "gastrointestinal ulceration effects" whereas claim 17 provides for toxic side effects of NSAIDS, which is broader than claim 1.[15] Applicant submits the claim revisions render this rejection moot.

Accordingly, Applicant requests the Office withdraw the 35 U.S.C § 112, second paragraph rejection of claims 17 and 20.

Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 17, and 20

Claims 1-5, 17, and 20 stand rejected under 35 U.S.C. § 103(a) as obviated by *Lai* (U.S. Pat. No. 5,916,910) and *Xing, et al.* (Dig. Disease Sci., 1990 Jan; 35(1):61-65). The Office stated that *Lai* provides for protective effects from modifying a pharmaceutically active agent, like anti-inflammatories, into a conjugate to lower side effects, like NSIAD topical ulceration.[16] The Office found the conjugates may be covalently linked by amide bonds, though *Lai* does not disclose using MAO-B inhibitors to reduce gastric ulcers.[17] *Xing, et al.* purportedly provides that MAO-B inhibitors deprenyl and pargyline attenuate gastric acid output, gastric mucosal injury, and gastric mucosal blood flow.[18] The Office then found *Xing, et al.* motivates the combination of aspirin with an MAO-B inhibitor, and concluded that one skilled in the art would be motivated to administer an anti-inflammatory like aspirin, chemically linked, mixed, or administered separately, with an MAO-B inhibitor with the expectation of reducing gastric ulceration.[19] Applicant submits that the combination fails to obviate the claimed invention because (1) a *prima facie* case of obviousness was not established; and (2) no reasonable expectation exists.

Lai and *Xing, et al.* cannot obviate the invention because a *prima facie* case of obvious has not been established. The Office propounded the findings as related above, and concluded that *Lai* and *Xing, et al.* would motivate one

> to administer an anti-inflammatory agent such as aspirin, that is chemically linked, physically mixed or administered separately, with a MAO B inhibitor,

[15] Page 5 of the non-final Office Action, dated December 8, 2011.
[16] Page 8 of the non-final Office Action, dated December 8, 2011.
[17] Pages 8-9 of the non-final Office Action, dated December 8, 2011.
[18] Page 9 of the non-final Office Action, dated December 8, 2011.
[19] Page 9 of the non-final Office Action, dated December 8, 2011.

> with a reasonable expectation of reducing gastric ulceration … because the prior art recognized a need to modify ulcerogenic active agents by co-administering another agent that is effective in reducing the known gastric side-effect…. Such reduction would reasonably enhance the beneficial anti-inflammatory effects of aspirin and provide gastric endothelial protection.[20]

Applicant notes that the findings do not show why one of skill in the art would select an MAO inhibitor for use in reducing gastric injury from NSAID administration. First, *Lai* discloses a pharmaceutically active agent is covalently attached to a nitric oxide scavenger.[21] The nitric oxide scavengers include dithiocarbamate, desferrioxamine, ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, hydroxypyridinones, pyridoxalisonicotinoylhydrazone, quercetin, 1,2-dimethyl-3-hydroxpyrid-4-one, phytic acid, and others.[22] The "pharmaceutically active agent" includes NSAIDS, analgesics, antianxiety agents, antidepressants, immunosuppressants, antimetabolite cytotoxics, antimigraine agents, and neuroprotective agents, like MAOB inhibitors.[23] As such, *Lai* provides for a NO scavenger with one of the agents, such as NSAIDS **or** MAO-B inhibitors. *Xing, et al.* "tested the hypothesis that administration of MAO B inhibitors produces an increase in central nervous system DA and NE concentrations … which is associated with **protection against cold water restraint (CWR)-induced gastric mucosal injury**, inhibition of basal gastric secretion, and basal gastric mucosal blood flow reduction."[24] This is also reflected in the abstract of *Xing, et al.*, which notes the MAO B inhibitors increase DA, NE and NACB and is associated with cold water restraint-induced injury. As noted previously, and reasserted below, the causes and type of ulceration differs between NSAID-induced ulcers and stress-induced ulcers. Because the references do not address the use of MAO inhibitors with anti-inflammatory drugs, not all the limitations of the claim are addressed by the references. Moreover, the Office's findings do not relate why one of skill in the art would find the use of the claimed invention obvious for treatment, prevention, and reduction in NSAID-induced gastrointestinal effects.

The Office's findings, stating that the references show protective gastrointestinal effects, do not provide a reason why one would consider articles disclosing stress-induced and

[20] Page 9 of the non-final Office Action, dated December 8, 2011.
[21] Lai(column 3, lines 60-67)
[22] Lai column 3, line 67 to column 4, line 7.
[23] Lai column 7, line 70 to column 21, line 53
[24] Xing, et al. Monoamine oxidase B inhibition reduces gastric mucosal blood flow, basal acid secretion, and cold water restraint-induced gastric mucosal injury in rats. Dig Dis Sci. 1990 Jan;35(1):61-5; page 62, column 1.

dopamine-induced ulceration to obviate the claimed invention. Applicant also respectfully points out that there is a link between the parasympathetic nervous system and stress-induced ulcerations,[25] therefore there is a link between brain function and stress-induced ulceration. Assertions of the perspective of a person of ordinary skill must be used in the obviousness inquiry, and require sufficient explanation such as providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[26]

> [W]hether or not stated explicitly, the perspective of a person of ordinary skill must frame the obviousness inquiry, and assertions of what such a person of ordinary skill would have found to be obvious require sufficient explanation to permit meaningful appellate review… [such as] providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[27]

Applicant asserts that the references fail to disclose the compositions for use with NSAIDs. Further, there is no evidentiary support or rationale to show how one skilled in the art would find the use compositions for different ailments, such as stress-induced ulceration, to obviate a method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs. Obviousness must be determined by comparing the differences between the claimed invention and prior art.[28] It is submitted the Office does not show how one of skill in the art would find these references obviate a method drawn to treating NSAID-induced ulceration, as provided in the claims. As noted above, NSAID-induced ulceration differs from stress-induced ulceration, which the art found may be linked to central nervous system's parasympathetic system.[29] Conversely, NSAID ulceration is caused by localized damage from the NSAID drug.

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[25] Caso, et al., The effects of physical and psychological stress on the gastrointestinal tract: lessons from animal models. Curr Mol Med. 2008 Jun;8(4):299-31, abstract; Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 Dec;99(6):2416-22. Epub 2005 Jul 28;abstract; page 2416, columns 1-2.

[26] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).

[27] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).

[28] MPEP 2141.02(I).

[29] Caso, et al., The effects of physical and psychological stress on the gastrointestinal tract: lessons from animal models. Curr Mol Med. 2008 Jun;8(4):299-31, abstract; Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 Dec;99(6):2416-22. Epub 2005 Jul 28;abstract; page 2416, columns 1-2.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious"[30] The Office stated that ""[o]ne of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the *results would have been predictable* to one of ordinary skill in the art."[31] The present invention provides cytoprotection to GI mucosa[32] through MAO inhibition by effects such as free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced blood flow, and stimulation of nitrogen oxide synthase.[33] Conversely, studies of existing cytoprotective anti-ulcer drugs have shown the drugs are "ineffective in preventing ulceration."[34] The Office's findings relating to MPTP-depletion induced ulceration and stress-induced ulceration do not show an adequate link to NSAID-induced ulceration, due to the differences in etymology and treatment. Therefore, Applicant submits the failure of the references to disclose the use of anti-inflammatory drugs is fatal to the obviousness determination.

The Office's findings also state that propargylamine derivatives "clearly demonstrate efficacy in reducing [gastric ulceration damage which] ... would reasonable enhance the beneficial anti-inflammatory effects of aspirin[.]"[35] Applicant respectfully traverses this finding as conclusory and lacking support. While the Office's findings relate to use of pargyline in stress-induced gastric injury, the findings do not relate to enhancing beneficial effects of anti-inflammatories.

Lai and *Xing, et al.* cannot obviate the invention because no reasonable expectation of success exists in light of the references. "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success."[36] Claim 1 provides

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[30] MPEP 2142.
[31] Page 11 of the non-final Office Action, dated Jan. 13, 2009 (emphasis added).
[32] See, page 18 of the Application ("the cytoprotective effect of MAO inhibitors in preventing and/or reversing the NSAID toxicity may be mediated by a combination of several cytoprotective actions[.]")
[33] Pages 17-18 of the Application.
[34] Nakashima, S., et al., Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin, World J. Gastroenterol. 2009 Feb 14;15(6):727-31, page 1, column 2.
[35] Page 9 of the non-final Office Action, dated December 8, 2011.
[36] MPEP 2143.02(I) (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986)).

> [a] method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs, comprising:
> administering to a subject an effective amount of monoamine oxidase (MAO) inhibitor;
> wherein the anti-inflammatory drug and MAO inhibitor are chemically linked, physically mixed or administered separately.

As ntoed above, the Office's findings relate to the association of MAO-B inhibitors on stress-induced gastric injury. Applicant submits that the art considers sources of gastrointestinal damage to be different from stress-induced ulceration and dopamine-depletion-induced ulceration. The etymologies of stress-induced ulceration, dopamine-deficient ulceration, and NSAID-induced ulceration are different, comprising different mechanisms of onset and treatment. NSAID-induced ulceration and damage, which occurs throughout the GI tract,[37] is "largely caused by the inhibition of COX1 and its role in normal mucosal defense mechanisms … and also through the inhibition of thromboxane A_2, which compromises platelet function and results in gastrointestinal bleeding."[38] NSAID damage occurs through topical and systemic effects, systemic are mainly by blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms, such as H_2S and NO reduction,[39] which "are two endogenously generated gaseous mediators important in maintaining gastric mucosal integrity that share many biological effects with prostaglandins."[40] COX-1 inhibition is believed to result in microvascular damage, restricting blood flow and causing tissue hypoxia and decreased mucosal resistance.[41] This causes increased mucosal permeability and myeloperoxidase activity, eventually causing gastric lesions.[42] NSAIDs increase endothelin-converting enzyme-1 (ECE-1) activity, upregulating endothelin-1 (ET-1), which results in suppressed cNOS and endothelial nitric oxide

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[37] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 495, column 2 (noting additional damage in such locations as small-bowel).
[38] Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 1-2.
[39] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1.
[40] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2 (also noting that cNOS and nNOS produce NO which functions in mucosal repair and ulcer healing depending on amount of NO); page 9, column 1 (noting an increase in NO during gastric ulcer healing).
[41] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1; page 7, column 2.
[42] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 1.

leading to loss of mucosal integrity in rats."[43] Acid diffusion through the mucosal barrier further destroys tissue and results in deeper necrosis and ulceration.[44]

NO is responsible for maintenance of gastric epithelium integrity and the mucus barrier,[45] and helps decrease acid secretion from parietal cells.[46] Importantly, "reduction in blood flow … thought to be the mechanism most responsible for NSAID-induced GI injury,"[47] caused by ICAM expression resulting in neutrophil adherence to the vascular endothelium[48] This is supported by studies which found "[m]ost NSAID-induced ulcers develop in the gastric antrum, which is also the site of greatest reduction in gastric mucosal blood flow. It has been suggested that this is because of focal ischaemia impairing the ability of the mucosa to withstand acid back diffusion leading to tissue injury."[49] Further, *Kim, et al.* showed decreased antral blood blow significantly correlated with gastric mucosal injury.[50]

> "Microvascular damage plays an early and critical role in the pathogenesis of NSAID-induced ulcers, underscoring the fact that the mucosal microvascular response is possibly the most important component of mucosal defence [sic]. The hyperaemic response to gastric acid is predominantly mediated by extrinsic sensory primary nerves … [resulting in] *subsequent nitric oxide-mediated vasodilation increasing submucosal blood flow*." [51]

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[43] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 2.
[44] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 6, column 2.
[45] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column1; page 2, column 2.
[46] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 2, column 2.
[47] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 1, column 1; page 2, column 1.
[48] Cryer, NSAID gastrointestinal toxicity. Curr Opin Gastroenterol. 2000 Nov;16(6):495-502; page 496, column 2; Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 3, column 1. See also, Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 5, column 1 (COX-1 depletion results in decrease in gastric mucosal blood flow, whereas COX-2 depletion promotes leucocyte adherence, and suppression of either COX enzyme in impaired gastric musocal- such as NO synthesis suppression or acid challenge- is ulcerogenic).
[49] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 7, column 2.
[50] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 8, column 1.
[51] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3; page 7, column 2 (emphasis added).

NO can limit or prevent blood flow reduction and block adherence of neutrophils to the vascular endothelium associated with NSAIDs.[52] This is supported by newly-developed COX-inhibiting, NO-donating drugs (CINODs), which have been developed in response to NSAID toxicity. The compoudns couple NO to an NSAID to improve GI safety.[53] Studies have found significantly reduced gastric damage compared to NSAIDs, when administered twice daily,[54] and increased blood flow and improved mucosal integrity.[55]

Conversely, stress induced ulcers are superficial and "clearly distinguished from … ulcers induced by drugs and from activation of a preexistent ulcer."[56] These stress-induced ulcerations do not possess an identified, definitive causative agent,[57] though "prolonged exposure to stress induces low-grade mucosal inflammation, leads to ultrastructural epithelial abnormalities and alters bacterial-host interactions including bacterial translocation[,]"[58] and alters ion secretion.[59] In fact, "*H. pylori* infection and NSAIDs are independent risk factors for peptic ulcer disease that have additive or synergistic effects on adverse gastrointestinal outcomes[.]"[60]Studies have found the nervous system plays an important role in stress-induced ulceration. Dopamine receptor DA1 "produces gastroprotection by several mechanisms, at least one of which is by reducing gastric acid output."[61] Melatonin affects stress-induced ulceration

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[52] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 1.
[53] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 1, column 2.
[54] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 1 (NO-naproxen (naproxcinod) compared to naproxen); page 4 column 2 to page 5, column 1.
[55] Lanas, Role of nitric oxide in the gastrointestinal tract. Arthritis Res Ther. 2008;10 Suppl 2:S4. Epub 2008 Oct 17; page 4, column 2 (NO-fluriprofen compared to fluriprofen).
[56] Silen, et al. The pathophysiology of stress ulcer disease. World J Surg. 1981 Mar;5(2):165-7.
[57] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; page 4 (citing Choung & Talley, Epidemiology and clinical presentation of stress-related peptic damage and chronic peptic ulcer. Curr Mol Med. 2008 Jun;8(4):253-7)
[58] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; pages 4-5 (citing a study by Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8) See also, Lutgendorff, et al. The role of microbiota and probiotics in stress-induced gastrointestinal damage. Curr Mol Med. 2008 Jun;8(4):282-98 (finding probiotic microbe populations shrink due to stress, allowing pathogenic microbes to grow).
[59] Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8; abstract. See also, Kitagawa, et al. Effects of water-immersion stress on gastric secretion and mucosal blood flow in rats. Gastroenterology. 1979 Aug;77(2):298-30 (suggesting that an elevation in gastric acid secretion without increase in mucosal blood flow causes gastric ulceration).
[60] Yuan, et al. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9; page 82, column 2.
[61] Glavin. Activity of selective dopamine DA1 and DA2 agonists and antagonists on experimental gastric lesions and gastric acid secretion. J Pharmacol Exp Ther. 1989 Nov;251(2):726-3; abstract.

through a mechanism involving the central nervous system,[62] and γ-aminobutyric acid (GABA) acts through peripheral receptors to reduce ulceration unrelated to gastric acid secretion.[63] Suppression of pentagastrin, an agonist of the cholecystokinin-B receptor which is expressed widely in the brain, stimulated gastric acid secretion by more than 90% prevented acid secretion and mucosal lesions.[64] Further, excessive peripheral sympathetic activity[65] and parasympathetic overactivity increase gastric acid output and contribute to stress-induced ulceration.[66] Increased vagus nerve activity was found to increase gastric choline acetyltransferase, acetylcholinesterase, and acetylcholine content, influencing gastric acid secretion.[67] Of interesting note, the vagus nerve, part of the parasympathetic system, was originally removed (vagotomy) as a treatment for peptic ulcers. The releasing factor for corticotrophin, a hormone and neurotransmitter, has been attributed as the main mediator of stress-induced damage,[68] and mast cells also influencing GI inflammation, evidencing that the brain-gut axis modulates the gastrointestinal immune system.[69]

Stress was also found to induce an increase in neutrophil infiltration in gastric mucosa, causing mucosal injury.[70] Inflammatory cytokines, such as IκBβ, NFκB, IL-1β, CINC-1, ICAM-1, and iNOS mRNA, increase linearly during stress. Neutralizing these cytokines reduced the activity of neutrophil reactive oxygen species, myeloperoxidase.[71] Stress induction increases reactive radicals causing protein oxidation and decreased glutathione content, with the severity of ulceration correlated with an increase in superoxide dismutase activity and decrease in

[62] Kato, et al., Central effect of melatonin against stress-induced gastric ulcers in rats. NeuroReport. 1997 July 7;8(9): 2305-9; abstract.
[63] Miñano, et al., Effects of GABA on gastric acid secretion and ulcer formation in rats. Life Sciences. 1987 Sept 28;41(13): 1651-8; abstract.
[64] Garrick, et al., Cimetidine and ranitidine protect against cold restraint-induced ulceration in rat by suppressing gastric acid secretion. Dig Dis Sci. 1987 Nov;32(11):1261-7.
[65] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2416, column 1.
[66] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2420, column 2; page 2421, column 2; abstract.
[67] Muramatsu, et al., Central regulation of gastric acetylcholine metabolism and acid output: analysis using stress and 2-deoxy-D-glucose administration in rats. Neurochem Int'l. 1986; 8(4): 553-8; abstract.
[68] Leza & Menchen. Stress-induced deleterious consequences in the gastrointestinal tract. Curr Mol Med. 2008 Jun;8(4):244-6; page 5 (citing a study by Gareau, et al. Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med. 2008 Jun;8(4):274-8).
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peroxidase activity.[72] Further, studies have shown that specific A_{2A} agonists reduce production of pro-inflammatory cytokines, limit neutrophil activation, and inhibit stress-induced gastric inflammation;[73] and gastric prostacyclin inhibited indomethacin-induced decreases in mucosal blood flow and inhibited leukocyte accumulation.[74] Administration of catechin inhibits release of gastrin, somatostatin, and histamine; and provides a protective effect against ulceration.[75]

There is also evidence that stress-induced damage occurs, at least in part, due to localized gastric ischemia. Models of stress-induced ulcer show an association between alternating regions of high blood flow and low blood flow in the gastric corpus and gastric tissue damage.[76] Administration of taurocholate uncouples oxidative phosphorylation of gastric mucosal mitochondria and inhibits ATPase, causing damage to the mucosa.[77]

As can be seen above, the art does not consider stress-induced ulceration to be the same as NSAID-induced ulceration. It is submitted that there are significant differences in the causes of damage, such as blocking COX-1 and COX-2, and other prostaglandin-independent mechanisms like H_2S and NO reduction for NSAID-induced ulcers,[78] or mucosal inflammation and excessive peripheral sympathetic activity[79] and parasympathetic overactivity for stress-induced ulcers. Likewise, eNOS activity has been found useful in addressing NSAID-induced ulcers, whereas iNOS has been seen to impact stress-induced ulcers. It is therefore submitted that one of skill in the art would not find it obvious to combine treatments for stress-induced ulcers for the treatment of NSAID-induced ulcers.

Furthermore, Applicant respectfully points out that MPTP is a neurotoxin precursor, not a therapeutic agent. MPTP is metabolized into 1-methyl-4-phenylpyridinium (MPP+) by MAO-B, which kills dopamine-producing neurons by interfering with complex I of the electron transport

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[72] Das, et al., Hydroxyl radicalis the major causative factor in stress-induced gastric ulceration. Free Radical Biol and Med. 1997; 23(1): 8-18; abstract.
[73] Odashima, et al., Selective adenosine A_{2A} receptor agonist, ATL-146e, attenuates stress-induced gastric lesions in rats. J Gastroenterol Hepatol. 2005 Feb;20(2):275-80; abstract.
[74] Harada, et al., Gastric prostacyclin (PGI2) prevents stress-induced gastric mucosal injury in rats primarily by inhibiting leukocyte activation. Prostaglandins Other Lipid Mediat. 1999 Jul;57(5-6):291-303; abstract.
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[77] Menguy & Masters, Mechanism of stress ulcer. Digestive Diseases and Sciences. 1976 Dec; 21(12): 1001-1007; abstract.
[78] Musumba, et al. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. Aliment Pharmacol Ther. 2009 Sep 15;30(6):517-31. Epub 2009 Jul 3, page 2, column 1; page 3, Table 1.

chain and causing a buildup of free radicals.[80] Assertions of the perspective of a person of ordinary skill must be used in the obviousness inquiry, and require sufficient explanation such as providing any evidentiary support or reasoning for why a person of ordinary skill in the field of the invention would have deemed it obvious to select and combine various steps from different references, in the manner of the applicant.[81] It is respectfully submitted that the Office has not articulated how the results from a neurotoxin, which destroy dopamine-producing neurons, are related to ulceration caused by anti-inflammatory drugs.

Accordingly, Applicant respectfully requests the 35 U.S.C. § 103(a) rejection of claims 1-5, 17 and 20 be withdrawn.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

By: /robert varkonyi/

Dated: March 8, 2012
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[79] Xie, et al., Role of parasympathetic overactivity in water immersion stress-induced gastric mucosal lesion in rat. J Appl Physiol. 2005 July 28; 99:2416-2422; page 2416, column 1.
[80] Richardson, et al., Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci. 2005; 88(1): 193-201; 193, column 2. http://en.wikipedia.org/wiki/MPTP (last accessed June 30, 2010).
[81] *In re Vaidyanathan*, 2010 WL 2000682, page 8 (Fed. Cir. 2010) (not precedential).

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

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